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17 MAY 93 09:55:39

U.S. Patent & Trademark Office

P0023

US PAT NO: 5,200,169 [IMAGE AVAILABLE]

L18: 1 of 2

DETD(36)

hydroxysuccinimide, or by conversion of a cyano precursor into an imidate ester. Such conversions can be considered as activating the molecule towards reaction with a corresponding functional group,. . .

DETD(36):

DETD(43)

Also provided are radiopharmaceutical kits for clinical use which include a vial or set of vials containing any of compounds I through VII, preferably bearing. . . the kit. The kit may also include one or more chromatographic columns or other suitable means for separating any remaining precursors and impurities from the radiohalogenated protein product.

DETD(43):

DETD(60)

To . . . is reduced to only aqueous. This material is used directly for protein labeling experiments, as described below. Alternatively, radioiodination with iodine-131 is carried out in like manner.

DETD(60):

DETD(66)

To . . . volume is reduced to only aqueous. This material is used directly for protein labeling experiments as described below. Radioiodination with iodine-131 is carried out in like manner.

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17 MAY 93 09:54:46 U.S. Patent & Trademark Office P0021

US PAT NO: 4,876,081 [IMAGE AVAILABLE] L18: 2 of 2

DETD(60)

DETDESC:

DETD(66)

To . . . volume is reduced to only aqueous. This material is used directly for protein labeling experiments as described below. Radioiodination with **iodine-131** is carried out in like manner.

=> d kwic

US PAT NO: 5,200,169 [IMAGE AVAILABLE] *Willbur* L18: 1 of 2

ABSTRACT:

Vinyl . . . II can be coupled to proteins such as monoclonal antibodies to provide reagents for diagnostic and therapeutic applications. Also metalated **precursors** of compounds I and II, as well as radiopharmaceutical reagent kits containing any of the subject small molecules.

SUMMARY:

BSUM(5)

Radionuclides of halogens possess properties that make them very attractive for both diagnostic imaging and radiotherapy. For example, radioiodine as **iodine-123** (T1/2=13 h, 159 keV gamma, electron capture) is nearly ideal for imaging with the current gamma cameras, and **iodine-131** (T1/2=8 d, 364 keV gamma, beta particle), while producing images of lower quality, has been demonstrated to be useful in. . . and bromine-77 (T1/2=2.4 d, several gammas, electron capture) has properties that make it attractive for radiotherapy. Other radiohalogens, such as **fluorine-18** (T1/2=110 min, positron) and astatine-211 (T1/2=7.2 h, alpha particle), are also attractive candidates for radioimaging and radiotherapy.

SUMMARY:

BSUM(16)

Also provided are metalated **precursors** of the foregoing radiohalogenated small molecules, as well as radiopharmaceutical reagent kits containing the subject radiolabeled and metalated small molecules.

DETDESC:

DETD(5)

As utilized herein, the symbol "*X" indicates any radioisotope of: **iodine**, particularly .sup.123 I, .sup.125 I, and .sup.131 I; bromine, particularly .sup.75 Br, .sup.76 Br, and 77.sup.Br ; fluoroine, particularly .sup.18. . .

DETDESC:

DETD(15)

Derivatized proteins also include glycoproteins treated with an **oxidizing agent** such as periodate to generate aldehyde groups on sugar units of the

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U.S. Patent & Trademark Office

P0022

US PAT NO: 5,200,169 [IMAGE AVAILABLE]

L18: 1 of 2

DETD(15) -

carbohydrate portion of the glycoprotein. Amine or hydrazine. . .

DETD(DESC):

DETD(18)

Also provided are radiohalogenated small molecules of formulas I and II wherein the Y substituent bears a precursor of the Z functional group. Suitable precursors include: carboxylic acid where Z is phenolic ester, imide ester, anhydride, acylsuccinimide, or maleimide; nitrile where Z is imide ester; . . .

DETD(DESC):

DETD(24)

The compounds of formulas VI and VII can be prepared by a number of methods, including hydrometalating the corresponding alkynyl precursor, substituting an organometallic group for a halogen on the corresponding vinyl halide precursor, or transmetalating the corresponding vinyl metal or organometallic compound. Compounds suitable for hydrometalating alkynyl precursors include: LiAlH_4 , $(\text{alkyl})_2\text{AlH}$, tri-n-butyltinhydride, SnMe_3H , Cl_3SiH , and $\text{Zr}(\text{cp})_2\text{HCl}$.

DETD(DESC):

DETD(25)

Two . . . The first method employs a hydrometalation reaction to metalate an alkynyl derivative bearing the functional group of Y or a precursor thereof. For example, the alkynyl derivative bearing the functional group of Y corresponding to compound iv above would be:

DETD(DESC):

DETD(27)

and a commercially available alkynyl derivative (Aldrich Chemical Co., Milwaukee, Wis.) bearing a precursor to the functional group of Y corresponding to compound iv above would be:

DETD(DESC):

DETD(31)

Suitable precursor molecules include: 4-pentynoic acid (Aldrich Chemical Company, Milwaukee, Wis.); 3,3-dimethyl 4-pentynoic acid (Helvetica Chimica Acta 51: 1663-1678, 1968); and 4-ethynyl. . .

DETD(DESC):

DETD(36)

Attaching . . . proteins will require the availability of a functional group Z, such as can be provided by conversion of a carboxylate precursor group into an ester containing a good leaving group, for example
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